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We salute Hoechst-Roussel Pharmaceuticals Inc. for their contribution to the Endowment Fund and for their continued support of clinical and investigative dermatology.

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In This Issue . . .

Update on an Immortalized Human Microvascular Endothelial Cell

The perceived importance of endothelial cells in human biology and medicine has increased dramatically in the last decade. These cells have critical functions in a wide variety of biologic processes including leukocyte trafficking, wound healing, inflammation, and tumor metastasis, and they have attracted the attention of biotechnology and pharmaceutical firms. They are attractive targets for gene-therapy strategies, and numerous attempts are underway to regulate the expression of cell adhesion molecules on endothelial cells. Amidst this flurry of activity it has been widely assumed that all human endothelial cells are alike, but recent information indicates clearly that microvascular endothelial cells differ in several biologically significant ways from large-vessel endothelial cells. Although over 13,000 articles have been written about endothelial cells in the last six years, only 26 have focused on microvascular endothelial cells, despite the fact that many or most physiologic and pathologic events that involve endothelial cells take place at the level of the microvasculature. In fact, many biologists would like to study the human microvasculature in detail, but the isolation of human microvascular endothelial cells is difficult, tedious, and expensive. In this issue, Xu *et al* (p. 833) provide an update on the characterization of the first immortalized human microvascular endothelial cell line, HMEC-1, originally described in the December 1992 issue of the *Journal* by Ades *et al* (*J Invest Dermatol* 99:683–690, 1992). These immortalized cells are inexpensive to culture and provide a limitless supply of cells. Most important, they retain almost all the characteristics of endothelial cells. In this issue, Xu *et al* flesh out the phenotypic and functional profile of these cells. Although this cell line does not perfectly recapitulate all the characteristics of microvascular endothelial cells from skin, it should prove to be very useful in understanding the role of the microvascular endothelium in human diseases.

Interleukin 7—A New Alternative in the Immunotherapy of Melanoma?

Immunotherapy with interleukin 2 (IL-2), which induces lymphocyte-activated killer (LAK) cells, has achieved some impressive regressions in patients with advanced melanoma who have not responded to conventional therapy, but the toxicity of IL-2, including pulmonary congestion, hypotension, and the capillary leakage syndrome, can be severe. IL-7, a recently described pre–B-cell growth factor that is involved in development of T lymphocytes, may hold some promise. In this issue, Schadendorf and co-workers (p. 838) compared the ability of IL-7 and IL-2 to induce LAK activity against human melanoma cells, keratinocytes, or endothelial cells. IL-7–induced LAK cells lysed human melanoma cells *in vitro* but were not as efficient as IL-2–generated LAK cells. Keratinocytes and endothelial cells, however, were not killed by IL-7–generated LAK cells alone, indicating that IL-7 has more specificity for melanoma cells, but were killed after addition of IL-2–induced LAK cells. The action of IL-2 on keratinocytes and endothelial cells, which may in turn be caused by TNF-α produced by administration of IL-2, may produce undesirable toxic side effects during IL-2 immunotherapy. TNF-α levels induced by administration of IL-7, however, are much lower than those produced by IL-2. IL-7 may be useful because it is more specific for melanoma cells, even though it is less effective against melanoma cells than IL-2. If IL-7–induced LAK activity alone is too weak for immunotherapy, the more discriminative killing spectrum of IL-7–generated LAK cells compared to IL-2–generated cells may be useful in the treatment of melanoma. Furthermore, combining the two cytokines might lead to reduced toxic side effects as well as to higher LAK activity against melanoma cells.

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Interleukin-4 — Chemotactic for Eosinophils in Atopic Dermatitis

Skin of patients with atopic dermatitis is infiltrated with T cells, and allergen-specific T cells have been cloned from lesional skin (*J Invest Dermatol* 97:389–394, 1991). *In vitro,* allergen-specific T cells are able to produce both IL-4 and IL-5 and are therefore considered to be of the Th2 phenotype. These findings suggest that T cells may be capable of releasing IL-4 in atopic skin. Although eosinophils are uncommon in atopic skin, deposits of eosinophil granular components are present, indicating that activated eosinophils have been present in the skin and have degranulated. No influx of neutrophils has been observed, however, suggesting a selective infiltration of eosinophils. This is usually explained by the effect of IL-4 on endothelial cells, because IL-4 induces the expression of endothelial cell adhesion molecules specific for eosinophils but not for neutrophils. Because IL-4 plays a predominant role in allergic inflammation and has been shown to be chemotactic for fibroblasts, Dubois *et al* (p. 843) investigated the effects of IL-4 on eosinophils. These investigators found that IL-4 also has the capacity to act directly on eosinophils, inducing a chemotactic response. In contrast to eosinophils from controls, which did not respond, eosinophils from patients with atopic dermatitis migrated toward a source of IL-4. This suggests that eosinophils infiltrating the tissue can be recruited to sites where high levels of IL-4 are present and may be further activated by IL-4 to release their toxic granular components. These experiments raise the possibility that interference with the secretion or action of IL-4 might decrease the toxic potential of infiltrating eosinophils in the tissue and thereby be helpful in atopic dermatitis.

A Mouse Model for Alopecia Areata

Aging C3H/HeJ mice develop focal, round areas of balding dorsal skin and diffuse hair loss on ventral skin that closely resembles the human disorder alopecia areata. Because C3H/HeJ mice are in general prone to developing autoimmune diseases, Sundberg's laboratory at the Jackson Laboratories in Bar Harbor, Maine, and King at Vanderbilt sought additional evidence that the condition resembled alopecia areata. Biopsies showed nonscarring alopecia limited to anagen-stage follicles and surrounded by mononuclear cells, similar to the human disorder. In the mouse, normal adult hair follicles remain in telogen for long periods, unlike human hair follicles, which are shed in a random, mosaic pattern and grow for much longer periods. New hair growth is initiated beginning at the head and progressively moves like a wave toward the tail. In mice with alopecia, only the anagen follicles in this wave of new hair growth are affected. Lymphocytes, primarily $CD8^+$ and to a less extent $CD4^+$ cells, infiltrate in and around the anagen follicles in affected C3H/HeJ mice, and the inflammation is associated with disruption of the inner and outer root sheath of the affected follicle. This produces a defective hair shaft that breaks off when it exits the follicle, giving rise to exclamation point hairs and other hair shaft abnormalities. These findings, described in this issue (p. 847), support the concept that the mouse model for alopecia areata is an autoimmune disease and that the immune cells around the hair follicles are responsible for inducing or maintaining abnormal hair growth. Also, hair regrows in response to intralesional steroid injections, a treatment commonly used for people with alopecia areata, supporting the similarity to alopecia areata and suggesting that the model can be used to develop and test new treatments for alopecia areata. Preliminary genetic studies suggest that the phenotype in C3H/HeJ mice is caused by several abnormal genes that have to work together (i.e., it is a polygenic trait). This mouse model provides a system in which investigations can be pursued in detail under strictly controlled circumstances, something that cannot be done with human volunteers.

IGF-I: An Important Regulator of Hair Follicle Growth and the Hair Growth Cycle *In Vitro*

In mammals hair growth is cyclical. Three distinct stages can be identified: an active growth state, anagen, during which hair growth occurs; an intermediate, regressive, catagen stage; and a resting state, telogen. The factors that regulate hair follicle growth and the hair-growth cycle are poorly understood, but it is likely that known growth factors play a role, and this possibility is under investigation in several laboratories. The insulin-like growth factors (IGF-I and II) are small diffusable factors similar to insulin in both structure and function. IGF-I has been shown to act as a mitogen for keratinocytes at physiologic concentrations, about 10^{-9} M, whereas insulin stimulates proliferation only at unphysiologically high concentrations on the order of 10^{-6} M. In this issue, Philpott *et al* (p. 857) have studied the effects of IGF-1 on intact hair follicles *in vitro* using a technique devised in Philpott's laboratory. They report that insulin at supraphysiologic concentrations (10 μg per ml, or about 10^{-6} M) can support human hair follicle growth and that in the absence of insulin these cultured hair follicles show premature entry into catagen. IGF-1, however, in the absence of insulin, not only stimulated hair follicles growth to the same extent as insulin but also prevented the premature entry into catagen; both effects were found at physiologic concentrations of IFG-1 (10 ng per ml, or about 10^{-9} M). IGF-II stimulated hair follicle growth in the absence of insulin and prevented premature entry into catagen, although not to the same extent as IGF-1 and only at higher a higher concentration (100 ng per ml). These studies show that IGF-1 is a potent growth factor for hair follicles and raise the possibility that IGF-1 may also play a major role in regulation of the hair-growth cycle.